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droplets substantially all of which are less than 1 micron in diameter in a continuous aqueous phase and in the absence of a polyoxypropylene-polyoxyethylene block polymer and without requiring muramyl peptides.

## REMARKS

### The Present Invention

The present invention relates to immunological adjuvants for use in increasing efficiency of vaccines and in particular to improved oil-in-water emulsions wherein substantially all of the oil droplets are less than 1 micron in diameter; and wherein the compositions do not require muramyl peptides and exits in the absence of any polyoxypropylene-polyoxyethylene block copolymer.

As discussed at page 3, line 32 to page 4, line 26 of the present application, there have been problems with prior anti-HSV gD formulations containing MTP-PE either because of lack of effectiveness or because an oil, such as IFA, was not approved for human use. In particular, some formulations were not effective in large animals, such as goats and baboons, even when they had been effective in small animals, such as guinea pigs. This illustrated the need for new adjuvant formulations that could be approved for human use and which would be effective in large animals.

The results of experiments set forth in the Examples 1-4 at pages 27-60 demonstrated that the claimed formulations, having oil droplets in the oil-in-water emulsion substantially all of which are less than 1 micron in diameter (formulation MTP-PE-LO-MF of the invention), were unexpectedly more effective in stimulating immune responses to molecular antigens in large animals (Example 3 and 4) as compared to similar formulations (Examples 1 and 2) containing oil and emulsifying agent but having oil droplets substantially larger than those of the invention (formulations MTP-PE and MTP-PE-LO of up 10 and 1-2 microns, respectively).

The Pending Claims

Claims 1-9, directed to improved adjuvant formulations suitable for stimulating immune responses to molecular antigens in large mammals, and claims 29-30, directed to methods of use, are pending in this application. Although Claim 29 described "submicron" droplets, the claim is amended to use the same language as claim 1 for consistency with regard to "substantially all which ar less than 1 micron in diameter."

Section 102(b) or 103

The Examiner's rejection of Claims 1-9 and 29-30 under 35 U.S.C. §102(b) or in the alternative under 35 U.S.C. §103 over Prigal (U.S. Patent 3,678,149) is hereby traversed.

Prigal describes water-in-oil emulsions which are therefore not the same as but different in kind from the oil-in-water compositions claimed in the present invention. Column 5 of the patent describes that the physical makeup of Prigal's emulsion consists of globules or particles of a dispersed phase (aqueous) surrounded by oil (continuous phase). This is an oil-in-water emulsion not an oil-in-water emulsion. Moreover, there is no teaching of emulsion formulations of oil-droplets substantially all of which are less than 1 micron in diameter. In fact, Prigal expressly teaches at column 6, lines 18-21 that the average particle size for relative stability is about 0.1 to 2 microns and for relatively faster rates of release from about 2-10 microns. Thus, there is no teaching of the either oil-in-water emulsions or the less than 1 micron size of substantially all of the droplets, which characteristics are unexpectedly useful in the present invention. Accordingly, Prigal does not anticipate the invention.

Prigal also does not suggest or make obvious the present invention. By contrast to Prigal, the present invention describes water as the continuous phase not oil as the continuous phase. One of skill in the art of adjuvants would not expect aqueous solutions or water-in-oil emulsions to have the same chemical, physiological or immunological properties as oil solutions or oil-in-water emulsions, much

less that any property of a formulation would differ in small versus large animals. Moreover, as discussed above, the results of experiments set forth in Examples 1-4 at pages 27-60 demonstrated that the claimed formulations, having oil droplets in the oil-in-water emulsion substantially of which are less than 1 micron in diameter (formulation MTP-PE-LO-MF of the invention), were unexpectedly more effective in stimulating immune responses to molecular antigens in large animals as compared to formulations containing oil and emulsifying agent, having oil droplets substantially larger than those of the invention (formulations MTP-PE and MTP-PE-LO).

For these reasons, Prigal neither anticipates nor makes obvious the present invention and the above rejections should be withdrawn.

The rejection of Claims 29-30 under 35 U.S.C. §102(b) or in the alternative under 35 U.S.C. §103 over Glass, et al. (U.S. Patent 3,919,411) or Cantrell (U.S. Patent 4,803,070) is respectfully traversed.

Glass, et al. relates to adjuvants comprising (1) a macromolecular synthetic resin complexing material capable of forming a complex with the medicinal agent at the N atoms thereon and tightly holding the agent thereby effecting slow release, and (2) an emulsion system carrier. The 26 columns of disclosure in Glass, et al. describe many characteristic of the chemical composition of the adjuvant formulation and the desired properties thereof. However, this extensive disclosure fails to describe the size of the droplets in the emulsions, much less teach that substantially all of the droplets are less than 1 micron in size. Accordingly, the claims are not anticipated by Glass, et al.

As discussed above, Glass, et al. describes many chemical characteristics of their adjuvant formulations. For example, Glass, et al. utilizes surfactant levels between 1 and 20% by volume. In column 6 of the patent, Glass, et al. states that the emulsion fails to form or is unsatisfactory for its intended use when the surfactant level is below 1% in the composition. In contrast, the present invention can usually be

effected by having the surfactant present in a preferred amount of 0.01 to 0.5% by weight (w/w). Column 6 of Glass, et al. describes that the oil generally must be at least 25 % v and the water content must be at least about 14 % v. Yet nothing is taught or suggested about the size of the droplets, much less that there should be a certain maximum size for "substantially all of the oil droplets of less than 1 micron in diameter" for more effective formulations in large animals. By being silent on the matter of size and providing extensive disclosure as to other characteristics of the composition, the disclosures of Glass, et al. point away from and fail to suggest the claimed formulations and their use. Absent the teaching of the present disclosure, it would not be obvious to use the oil droplet size of the claims in order to enhance the immunogenicity of the adjuvant composition.

In view of the above discussion, Glass, et al. neither anticipates or makes obvious the method of the instant invention and the rejections based on Glass, et al. should be withdrawn.

Cantrell teaches a method of preparing adjuvants effective as immunopotentiators for polysaccharide antigens. Cantrell's emulsion, either lipid or oil-in-water, contains the polysaccharide antigen and a bacterial adjuvant in a particulate form. However, Cantrell neither recognizes nor discloses the use of any advantageous oil particle size.

In fact, it does not appear that any of the methods used by Cantrell result in particles of the size in the present claims. In columns 3 and 4, Cantrell describes various methods of blending the liquid emulsion in a vortex machine, motor-driven pestle or blender until a milky white emulsion is obtained. This is not the same as Applicant's invention which recognizes and enables preparation of submicron oil droplets as immunopotentiators in an adjuvant composition. It is clear that Cantrell did not recognize or suggest the use of submicron oil particles to increase the effectiveness of the immunogenic agent. Therefore, Cantrell does not teach or suggest the present invention to one of skill in the art.

Moreover, Cantrell's adjuvant additionally requires the presence of a refined detoxified bacterial endotoxin obtained from Re mutant strains of Salmonella. Such endotoxins are not required by the present invention.

Accordingly, for all of the above reasons, the rejections based on Cantrell should be reconsidered and withdrawn.

Moreover, with regard to either Glass, et al. or Cantrell, the results of experiments set forth in Examples 1-4 at pages 27-60 demonstrated that the claimed formulations, having oil droplets in the oil-in-water emulsion substantially all of which are less than 1 micron in diameter (formulation MTP-PE-LO-MF of the invention), were unexpectedly more effective in stimulating immune responses to molecular antigens in large animals as compared to formulations containing oil and emulsifying agent, having oil droplets substantially larger than those of the invention (formulations MTP-PE and MTP-PE-LO).

Accordingly, the claimed formulations and use are not anticipated or made obvious by either Glass, et al. or Cantrell.

Obviousness Double-Patenting

Claims 1-9 and 29-30 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the claims of USSN 07/357,035. This rejection should be withdrawn in view of the Official notice dated December 19, 1991 that 07/357,035 is now abandon.

The application is considered in good and proper form for allowance and the Examiner is respectfully requested to process this application to issue.

If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject

application, the Examiner is invited to call the undersigned at (415) 494-7622.

Respectfully submitted,

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